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Oseltamivir-resistant 2009–2010 pandemic influenza A (H1N1) in an immunocompromised patient

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Abstract

Although neuraminidase inhibitors are active against most 2009–2010 pandemic influenza A (H1N1) swine-origin strains, sporadic cases of oseltamivir resistance have been described. Since April 2009, 54 cases of oseltamivir-resistant H1N1 swine-origin have been reported in the USA (<http://www.cdc.gov/flu/weekly/>; accessed 1 February 2010). Approximately 1.4% of tested isolates are oseltamivir resistant. We report a patient with an underlying hematological malignancy who was hospitalized with influenza A (H1N1) swine-origin and whose strain developed oseltamivir resistance during therapy.

Keywords: H1N1, immunocompromised, influenza A, oseltamivir, resistance

Original Submission: 14 February 2010; **Accepted:** 1 March 2010

Editor: D. Raoult

Article published online: 10 March 2010

Clin Microbiol Infect 2010; **16**: 1576–1578

10.1111/j.1469-0691.2010.03212.x

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A 26-year-old female with pre-B acute lymphocytic leukaemia was admitted to our hospital on November 18, 2009 for re-induction chemotherapy. She was started on high-dose cytarabine, L-asparaginase, acyclovir and trimethoprim-sulphamethoxazole. On admission, her absolute neutrophil count (ANC) was 800 cells/ μ L. On hospital day 3, she developed a nonproductive cough and had a temperature of 102.6°F with an ANC of 300 cells/ μ L. She was started on vancomycin, cefepime and oseltamivir 75 mg twice daily. One of two blood cultures grew α -haemolytic streptococci. A nasopharyngeal swab sent for respiratory viral panel testing (xTAG[®] RVP; Luminex Corp., Austin, TX, USA) revealed influenza A (H1N1), nonsubtypeable probable swine-origin and rhinovirus (Table 1). On hospital day 8, she had a temperature of 103.6°F and posaconazole and meropenem were added, oseltamivir was continued, and cefepime was stopped. Chest computed tomography (CT) demonstrated patchy airspace disease in the right lung consistent with pneumonia. Fevers continued and several blood and urine cultures were negative. A bronchoscopy performed on hospital day 11 revealed negative cultures for aerobic, anaerobic, and acid-fast

TABLE 1. Influenza A (H1N1) testing

Hospital day of specimen collection	Specimen source	RVP assay	Culture	H275Y mutation testing ^a
3	NP	Influenza A H1N1, swine-origin	Influenza A	Negative
11	Bronchoscopy	NA	Influenza A	Positive
17	NP	Influenza A H1N1, swine-origin	Influenza A	Positive
20	NP	Negative	NA	NA

NP, nasopharyngeal; NA, not available; RVP, respiratory viral panel.

^aResistance testing performed on hospital day 17 returned on hospital day 23. Isolates from hospital day 3 and 11 were subsequently tested for the H275Y mutation (ViraCor, Lee's Summit, MO, USA).

bacteria, legionella and fungi. Direct-fluorescent antibody testing for *Pneumocystis jiroveci* was negative. A viral culture derived from the bronchoscopy specimen grew influenza A (H1N1) swine-origin. The patient continued to have daily fever in the setting of prolonged neutropenia, and lipid-formulation amphotericin B (Abelcet; Enzon Pharmaceuticals, Bridgewater, NJ, USA) was added with discontinuation of the posaconazole. Urine legionella antigen and galactomannan assays were negative. On hospital day 14, the patient was transferred to the intensive care unit for refractory hypotension. She developed diarrhoea and doxycycline and metronidazole were added. The patient stabilized within 24 h and was transferred back to a medical unit. On hospital day 17, a nasopharyngeal swab again revealed H1N1, as well as rhinovirus, despite 13 days of oseltamivir. A repeat chest CT scan showed worsening right lung infiltrates. A concern for oseltamivir-resistance was raised. The patient was changed to zanamivir, two inhalations twice daily, and a nasopharyngeal swab was sent for resistance testing (ViraCor, Lee's Summit, MO, USA). Fevers continued. *Clostridium difficile* toxin testing was negative. Doxycycline and metronidazole were discontinued and amphotericin B was changed to posaconazole. A transthoracic echocardiogram performed on hospital day 17 revealed severe left ventricular dysfunction with an ejection fraction of 20%. An echocardiogram in 2008 was normal. It was unclear whether the cardiomyopathy was secondary to chemotherapy (cumulative lifetime anthracycline dose of 317 mg) or viral myocarditis. A nasopharyngeal swab sent for respiratory viral panel testing on hospital day 20 was negative. On hospital day 23, a nasopharyngeal swab performed on hospital day 17 was found to be positive for oseltamivir-resistant influenza A with the H275Y mutation. Zanamivir had been discontinued after 5 days. A repeat bedside transthoracic echocardiogram demonstrated moderate pericardial effusion without tamponade and a left ventricular ejection fraction recovered to 65%. Despite aggressive therapy, she died on hospital day 40. An autopsy was not performed. After her death, we performed resistance testing on a stored sample of the initial influenza strain isolated on hospital day 3, which was sensitive to oseltamivir. Additional testing was also performed on the bronchoscopy specimen from hospital day 11, which demonstrated that resistance to oseltamivir had developed after 8 days of oseltamivir therapy.

To our knowledge, this is the first case of oseltamivir-resistant, swine-origin influenza A (H1N1) associated with a fatal outcome. Despite widespread use of oseltamivir for prophylaxis and treatment during the 2009–2010 influenza season, resistance to this agent is relatively rare [1–4,5–7]. In the USA, 42 of 52 individuals with resistance had documented exposure to oseltamivir (<http://www.cdc.gov/flu/>

weekly; accessed 1 February 2009), suggesting that most cases of resistance in the USA developed under selective pressure to the drug. Resistance developed during oseltamivir treatment in our patient who was receiving 75 mg twice daily. The recent literature suggests that an increased dose of 150 mg twice daily may be preferable for critically ill patients [8]. The most commonly reported mutation associated with oseltamivir-resistant H1N1 swine-origin is the H275Y mutation [9–12]. Resistance may develop more commonly in immunocompromised patients [6], particularly those with haematological malignancies [2,13]. Mortality from seasonal influenza in immunocompromised patients is high [12]. However, we are unaware of reported cases involving oseltamivir-resistant, H1N1 swine-origin associated with death, including immunocompromised patients. Resistance testing should be carried out in H1N1 swine-origin infected, immunocompromised patients who fail to respond appropriately to antiviral therapy. Higher dosing of oseltamivir at 150mg twice a day should also be considered in these patients.

Transparency Declaration

The current study received no financial support. All authors declare that they have no conflicts of interest.

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